UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,293	08/01/1997	MAE JOANNE ROSOK	030436.46SU1	5228

23914 7590 08/14/2002

STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	29

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/905,293	Rosok et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 5, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above, claim(s) *23-27 and 32-52* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-22 and 28-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Appeal Brief

1) Acknowledgment is made of Applicants' Appeal Brief filed 07/05/01 (paper no. 28) in response to the final Office Action mailed 08/31/99 (paper no. 12).

Prosecution Reopened

2) In view of the Appeal Brief filed, an Appeal Conference was conducted in the instant case. Following the Appeal Conference, it was decided that the PROSECUTION be REOPENED in the instant application. New and/or modified grounds of rejection(s) are set forth below. To avoid abandonment of the application, Appellants must exercise one of the following two options:

(a) File a reply under 37 C.F.R 1.111 (if this Office action is non-final) or a reply under 37 C.F.R 1.113 (if this Office action is final); or,

(b) Request reinstatement of the Appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 C.F.R 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 C.F.R 1.193(b)(2).

Status of Claims

3) Claims 1-52 are pending in the instant application.

Claims 1-22 and 28-31 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Drawings

6) This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 C.F.R 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must

arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, Applicant should file corrected drawings as soon as possible. Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Specification

7) The instant specification is objected to for the following reasons:

(a) The use of the trademarks in the instant specification has been noted in this application. For example, see page 46, line 7: page 20, line 9: "Tween 80"; page 20, line 10: "Triton WR-1339" and "Triton A-20"; "Sequenase"; and page 29, line 20: "Immunlon2". The recitation(s) should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

(b) On page 48, line 25, it is unclear what do Applicants mean by "previous patent". Clarification is requested.

Applicants' Arguments

8) In the Appeal Brief, Applicants in essence assert that Morgan *et al.* teach alterations in the N-terminal region of CH2 that reduce toxicity. Applicants contend that Morgan *et al.* (WO 94/29351) ('351) is not prior art, because Morgan *et al.* provide 'no data on immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy". Applicants state that in contrast, Applicants' *in vivo* data from Example 3 shows that alterations in multiple toxicity associated domains in the constant region "inhibit immunoglobulin-induced toxicity that results from immunotherapy".

Applicants' arguments have been carefully considered. The art rejections are currently withdrawn in light of the scope of enablement rejection(s) made below. It should be noted that the recitation "multiple toxicity associated domains in the constant region" in the instant base claims 1-3 and 5 is **not** limited to the CH2 domain. None of the claims under examination identify the "multiple toxicity associated domains in the constant region" as containing any specific portions of the CH2 domain, C-terminal and N-terminal regions of the CH2 domain, or regions of the CH2 domain comprising amino acids 231-238 and amino acids 310-331. As acknowledged by Applicants on page 3 (see first full paragraph) of the Appeal Brief, alterations in multiple amino acids in a single toxicity associated domain in the constant region is encompassed within the instant invention as well (see also lines 21 and 22 on page 4). Furthermore, as described below in paragraph 27, Example 3 provides no data on "immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy". The *in vivo* demonstration via Example 3 is limited to a showing that a CH2-containing domain of the BR96 antibody is associated with the induction of acute gastroenteropathy in dogs and that a BR96 antibody which does not contain CH2 domain does not cause acute gastroenteropathy.

Rejection(s) Withdrawn

9) The rejection of claims 1, 2, 5 and 7-10 made in paragraph 13 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C § 102(b) as being anticipated by Morgan *et al.* (WO 94/29351) is currently withdrawn in light of the issues raised in the instant Office Action with regard to the scope of the limitations: "toxicity associated domains in the constant region" and "toxicity associated domains in the CH2 domain".

10) The rejection of claims 3, 4, 6 and 11-22 made in paragraph 15 of the Office Action mailed 02/11/99 (paper no. 9) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) as applied to claim 1 or 2 above, and in view of Yelton *et al.* (US 5,792,456) or Muroi *et al.* (*Blood* 79: 713-719, 1992, abstract) taken with Gillies *et al.* (*Human Antibodies and Hybridomas* 1: 47-54, 1990) is currently withdrawn in light of the issues raised in the instant Office Action with regard to the scope of the limitations: "toxicity associated domains

in the constant region" and "toxicity associated domains in the CH2 domain".

11) The rejection of claims 28-31 made in paragraph 16 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) as applied to claims 1 or 5 above, and further in view of Yelton *et al.* (US 5,792,456) is currently withdrawn in light of the issues raised in the instant Office Action with regard to the scope of the limitations: "toxicity associated domains in the constant region" and "toxicity associated domains in the CH2 domain".

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) Claims 1-3, 5-22 and 28-31 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regards as the invention.

(a) Claim 6 is vague and indefinite in the recitation: "domains in the CH2 domain" (see lines 5 and 6), because it is unclear how 'domains' can be present in a 'domain'. It is unclear what is encompassed in the limitations, "domains" and "domain". What part of the immunoglobulin constitutes "domains in the CH2 domain" is unclear.

(b) Claims 1-3, 5 and 6 are vague and confusing in the recitation "toxicity associated domains". It is unclear in what way this recitation differs from the limitation "toxicity associated regions" in claim 4.

(c) Claims 5 and 6 are confusing in the recitation: alleviating symptoms associated with the disease, "the structural alteration of the constant region" thereby preventing..... It is unclear what purpose the recitation "the structural alteration of the constant region" serves in this part of the claims.

(d) Claim 7 lacks antecedent basis for the recitation: "method of claim 1, 2, 3, 4, 5 or 6, wherein **the** portion" [Emphasis added], because claims 1-6 do not recite any "portion".

(e) Claims 8-10, 15-22 and 29-31, which depend from claims 5 or 6, are also rejected as being indefinite, because of the vagueness or indefiniteness identified above in the base claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph

13) Claims 1-3, 5, 8-22 and 28-31 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant base claims include the limitation "multiple toxicity associated domains" wherein the structural alteration is to be effected. The description for 'multiple toxicity associated domains" on page 10, lines 8-15 of the specification describing 'at least two ... domains', one 'roughly' localized to 231-238 and another roughly localized to amino acids 310-331, is non-limiting. The instant claims do not recite the specific 231-238 and 310-331 amino acids as the "multiple toxicity associated domains". The description on page 10 is not limited to the constant region of an immunoglobulin molecule. The broad description "at least two toxicity associated domains" on page 10 of the specification means that more than two 'domains', i.e., CH1, CH2, CH3, and possibly VH and VL domains, are encompassed in the scope. This part of the specification states as follows:

> As used herein the terms "multiple toxicity associated domains" means more than one discrete toxicity associated domain. As there appear to be **at least two toxicity associated domains** in the immunoglobulin molecule, **one roughly localized to amino acids 231-238** and **another roughly localized to amino acids 310-331**, an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues **in both of these domains**. This definition excludes structural alterations targeting a single toxicity associated domain. [Emphasis added].

The art-known meaning or definition of an immunoglobulin 'domain' is contrary to the one described in the instant application. The written description in the instant specification which refers to amino acid residues 231-238 and amino acid residues 310-331 respectively as 'domains' is contrary to what the art recognizes as 'domains' in an antibody molecule. For instance, Figure 1 of Winter *et al.* (US 5,648,260) depicts VL, VH, CH1, CH2 and CH3 as the "domains" ([ ]) of an immunoglobulin molecule.

Since any toxicity-associated domains of an immunoglobulin are encompassed in the scope of the claims wherein the structural alterations are to be effected, a precise meaning and a

closed definition for the term 'domains' is critical or essential to the practice of the invention, but is not included in the claim(s) or the specification. The feature of effecting structural alterations in the toxicity-associated 'domains' is considered essential by Applicants which supposedly makes Applicants' altered immunoglobulin or method novel or non-obvious. However, the non-limiting description on page 10 is contrary to the art-recognized description, and therefore one of ordinary skill in the art cannot perform the structural alteration in an immunoglobulin without a clear written description. One of ordinary skill in the art cannot envisage the scope, i.e., what domains or specific amino acids are embraced by the claims wherein structural alterations are to be effected. From the art-recognized description, it is clear that amino acid residues 231-238 and 310-331 do not constitute 'domains', because these amino acids are not contained in separate CH or variable 'domains' of the immunoglobulin molecule. The lower panel of Figure 26 of the instant application, for example, shows that amino acid residues 231-238 and 310-331 are contained within one constant region domain, i.e., CH2 domain. Although Applicants can be their own lexicographers, Applicants cannot interpret a term in a way that is contrary to the meaning or definition provided by those skilled in the art. With a specification that contains no precise written description or a description that is contrary to what the art teaches, one of ordinary skill in the art would not be able to make and use the invention, without undue experimentation.

14) Claims 1-22 and 28-31 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of avoiding immunoglobulin-induced acute GI toxicity in a mammalian subject comprising administering the BR96 immunoglobulin molecule having a variable region and a constant region to the subject, the BR96 immunoglobulin being modified prior to administration by structurally altering the BR96 antibody by deleting the CH2 domain of BR96, does not reasonably provide enablement for a method of inhibiting or preventing immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy comprising administering any modified immunoglobulin molecule that is structurally altered in any domain of the constant region other than the CH2 domain and in any way other than deletion

so that the immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy is inhibited or prevented, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988)* as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the claimed method of inhibiting or preventing immunoglobulin-induced toxicity 'resulting from immunoglobulin immunotherapy' comprising administering to a subject a structurally altered immunoglobulin is **required** to be carried out in a subject who has necessarily undergone a target-specific immunoglobulin therapy and is suffering from immunoglobulin-induced toxicity as a result of such therapy. Example 3 is the only example in the instant specification which describes an *in vivo* experiment performed using dogs. The structurally altered immunoglobulin administered to three dogs is a tumor-specific CH2-deleted chimeric BR96, cBR96-A, which has been mildly reduced and alkylated. The route of administration is not disclosed. Two control dogs which received the mildly reduced and alkylated chimeric BR96 experienced the typical GI toxicity, whereas three dogs that received the CH2-deleted BR96 did not display GI toxicity. The dogs that were included in the experiment of Example 3 were **not** pre-administered with any target- or tumor-specific immunoglobulin, or subject to an immunoglobulin therapy such that the Ig therapy induced toxicity in these dogs, prior to the administration of the CH2-deleted BR96. The dogs are not disclosed as having any disease being associated with a target to which BR96 or cBR96-A binds, or associated with any

immunoglobulin-induced toxicity resulting from immunoglobulin therapy. The dog experiment is thus limited to a demonstration that normal dogs administered with the CH2-deleted BR96 showed no acute GI toxicity, whereas dogs administered with the structurally unaltered BR96 antibody experienced typical GI toxicity. Therefore, the method that is being claimed in the instant claims is not what is enabled via Example 3. The instant specification does not enable a method of inhibiting or preventing immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy for any specific disease. In Example 3, the CH2-deleted BR96 was not administered to dogs that were suffering from toxicity induced by a pre-administered immunoglobulin, which Ig recognized and bound to a target, the target being associated with any specific disease for example, cancer, cardiovascular diseases, neurological diseases, dermatological diseases or kidney diseases. The *in vivo* demonstration via Example 3 is limited to a showing that a CH2-containing domain of the BR96 antibody is associated with the induction of acute gastroenteropathy in dogs and that a BR96 antibody which does not contain CH2 domain does not cause acute gastroenteropathy. Thus, there is no showing that the CH2-deleted BR96, when administered to a subject suffering from any one of the above-cited diseases and has been treated with a toxicity-inducing immunoglobulin specific to the disease target such that the target-specific Ig induces Ig-associated toxicity in the subject, would inhibit or prevent the Ig-induced toxicity in the subject.

The instant specification further describes that, of the three constant region domains in an antibody, C_H1, C_H2 and C_H3, the second constant region domain, C_H2, contains sequences associated with effector functions of the antibody, i.e., sequences responsible for complement fixation and Fc receptor binding. See paragraph bridging pages 2 and 3 of the instant specification. The specification further describes that a deletion of the entire 'C_H2 domain' may render the molecule unable to: i) bind an Fc receptor thereby eliminating the antibody's possibility of mediating antibody-dependent cellular cytotoxicity (ADCC); and ii) bind C1q; or iii) activate complement. See paragraph bridging pages 10 and 11. This is evidence that each of the discrete toxicity is associated with **one** constant region domain, C_H2, of an antibody

molecule, and that the multiple toxicity-associated regions are contained within one domain in the constant region, i.e., C_H2 domain. That the two stretches of amino acid residues recited in the second paragraph on page 10, i.e., 231-238 and 310-331, are present within the C_H2 domain is evident from the lower panel of Figure 26. However, the claims as recited currently, encompass a method that uses an immunoglobulin that has structural alteration in any domain of the constant region, including the C_H1 and/or C_H3 domains. Clearly, a method as recited that uses BR96 or any other immunoglobulin containing structural alteration(s) in C_H1 and/or C_H3 domains of the constant region is not enabled. Neither the instant specification nor the state of the art has established that multiple toxicity-associated regions are present in any other domain other than the C_H2 domain of an immunoglobulin. Identification of multiple toxicity-associated non-C_H2 domains in an immunoglobulin molecule alone would require undue experimentation by one of ordinary skill in the art.

Given the lack of disclosure and/or specific guidance in the specification, the breadth of the claims, the absence of working examples enabling the full scope of the claims, and the quantity of experimentation necessary, one of ordinary skill in the art could not reproducibly practice the invention commensurate in scope with the claims, without undue experimentation. Therefore, the claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Relevant Prior Art

15) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Winter *et al.* (US 5,648,260) expressly disclose that alteration in amino acid residues 234, 235, 236 or 237 and alteration of any one of residues 318, 320 and 322 abolish Fc receptor binding and C1q binding functions of an antibody. Winter *et al.* teach the *in vivo* therapeutic applications of altered antibodies in man and animals (see column 5, full paragraphs 1 and 3-7; and column 6, full paragraphs 4, 6, 7 and 10; and column 9, paragraphs 3 and 4).

Morgan *et al.* (US 6,180,377, filed 03/25/1996) disclose humanized antibodies

structurally altered in one or more amino acid residue in the CH2 domain of the constant region, such as, Leu235 and/or Gly237, or within amino acid positions 231-239, or 234-239, and their therapeutic *in vivo* use in appropriate doses (see entire document).

- Morgan *et al.* (WO 94/29451) disclose a method of therapy comprising administering to a human or an animal an effective amount of a recombinant antibody (see claim 18). The antibody is humanized and has the C_H2 domain replaced, i.e., altered (see page 4, third full paragraph). The term 'altered' represents the substantial decrease in the ability of antibody to fix complement compared to the starting unaltered antibody by altering an appropriate amino acid, for example, an amino acid at position 235 **and**/or 237. Figure 18 shows that the chimeric and CDR grafted IgG1 containing the structural alteration, L235E, inhibits antibody-dependent complement mediated cytotoxicity. The immunological diseases that are treated with the CH2-altered antibody include neurological diseases, skin diseases, gastrointestinal tract diseases etc. The antibody administered orally would be well tolerated by the patient's digestive system. The dose and routes of administration are taught (see pages 14-16).

- Schreiber *et al.* (*Cancer Res.* 52: 3262-3266, 1992 - Applicants' IDS) teach a method of reducing or eliminating ADCC or CDC in mice with tumors comprising administering an effective amount of $F(ab')_2$ fragments of the anti-tumor monoclonal antibody, BR96. Mice receiving BR96 $F(ab)_2$ were without palpable tumors at the end of the treatment (see entire document).

Objection(s)

16) In claims 1-6, for clarity, it is suggested that Applicants replace the recitation "toxicity associated domains" with the recitation --toxicity-associated domains--.

Remarks

17) Claims 1-22 and 28-31 stand rejected.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the

Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

19) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. DEVI, PH.D.
PRIMARY EXAMINER

August, 2002

L. F. Smith

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600